

## Selenium Accumulation in Plant Foods

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*Selenium (Se) is an essential nutrient, and Se deficiency is associated with disease conditions and general impairment of the immune system. Supplementation of Se to humans already consuming the RDA may help to prevent certain cancers. A convincing argument can be made for augmenting the food supply with Se, and Se-enhanced plants may be the best means of accomplishing this. Plants accumulate varying amounts of Se in different chemical forms; some plants accumulate Se in direct relationship to the amount available from the soil, whereas others (Se-accumulators) may accumulate Se in concentrations many orders of magnitude above that in the soil. There are many different chemical forms of Se in plants, and the form partially dictates the metabolism of Se by the animal that consumes the plant. The Se content and the chemical form of Se within plants may be altered by manipulation of plant genetics or by agricultural production conditions. However, attempts to maximize Se in plants may have unintended consequences and must be carefully monitored.*

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### INTRODUCTION

The benefits of selenium (Se), an essential nutrient, and the functional consequences of Se deficiency are well established and have been extensively reviewed.<sup>1</sup> The daily requirement for Se in adults (55 µg) is readily met by most North Americans, but large numbers of people in Europe, Asia, and parts of Africa have intakes

of less than the Recommended Daily Allowance (RDA). Se deficiency has been associated with impairment of the immune system. As seen in parts of China, very low intakes (<25 µg/d) may contribute to a juvenile cardiomyopathy (Keshan disease) that is preventable by Se supplementation. Se intakes of 25 to 50 µg/d is common across much of Europe. Such low intakes do not cause frank Se deficiency, but the implications for health are not clear and some professionals have voiced concern.<sup>2</sup>

Se intakes greater than the RDA may be beneficial. Clark et al.<sup>3</sup> conducted a 13-year, placebo-controlled, randomized, double-blind clinical trial that supplemented 1312 older Americans with either a placebo or 200 µg/d Se (as Se-enriched yeast). The Se-treatment group exhibited significantly lower incidences of cancer mortality and overall cancer rate, with specific decreases in cancers of the prostate, lung, and colon/rectum.

The present evidence indicates that increasing Se intakes in populations with overt Se deficiency, as well as in populations already consuming Se-adequate diets, may improve health and reduce health care costs. Increasing the Se content of foods is an excellent means of accomplishing this goal, and plants may offer the best opportunity to do so.

### SE BIOCHEMISTRY

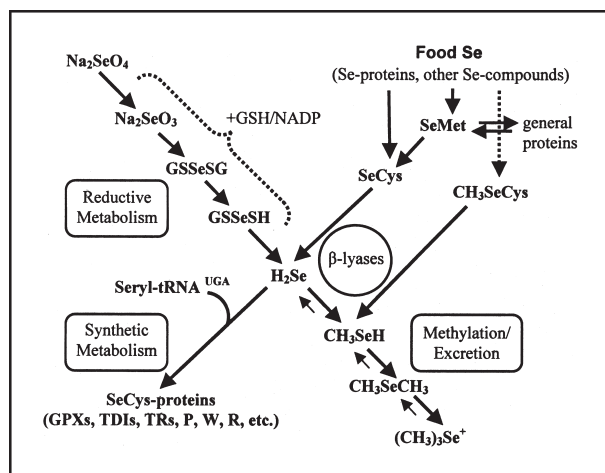
Se is covalently bonded in multiple organic molecules, and the chemical form that is ingested affects its potential metabolism. Foods contain diverse amounts and chemical forms of Se, so Se metabolism will be determined in part by the food consumed. A simplified scheme of Se metabolism in animals is depicted in Figure 1 (for a detailed review of Se metabolism in animals, see Ganther and Lawrence, 1997<sup>4</sup>). Inorganic salts of Se (e.g., selenite, selenate) enter a reductive pathway that results in the formation of selenide. Se can be bound in seleno-derivatives of methionine (Met) and cysteine (Cys), and, during protein synthesis, selenomethionine (SeMet) may randomly substitute for Met. Alternatively, SeMet may be converted to selenocysteine (SeCys), which may then be cleaved by a specific lyase, forming selenide. Selenide may be metabolized by one of two pathways. One pathway is methylation, which ulti-

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**Figure 1.** Metabolism of biologically important selenomolecules. Selenomethionine (SeMet) can be incorporated into proteins because it readily acylates methionine (Met)-tRNA. Alternatively, it can be converted to selenocysteine (SeCys) through the transsulfuration pathway. SeCys can then be degraded to hydrogen selenide ( $\text{H}_2\text{Se}$ ) by a specific lyase enzyme. Se-methylselenocysteine ( $\text{CH}_3\text{SeCys}$ ) is degraded by a lyase to methylselenol ( $\text{CH}_3\text{SeH}$ ). In contrast, selenite is metabolized to  $\text{H}_2\text{Se}$  via selenodiglutathione (GSSeSG, SDG) and glutathione selenopersulfide (GSSeSH).  $\text{H}_2\text{Se}$  is generally regarded as the precursor for supplying Se in the active form for the synthesis of selenoproteins. Further metabolism of  $\text{H}_2\text{Se}$  involves sequential methylation by S-adenosylmethionine to  $\text{CH}_3\text{SeH}$ , dimethylselenide, and trimethylselenonium.

mately results in excretion through the urine or breath. Limited evidence suggests that the mono-methylated Se intermediate is a potent anti-cancer metabolite.<sup>4</sup> In the other pathway, selenide may be used to form SeCys, which is inserted into selenoproteins, where the redox potential of Se allows it to catalyze multiple reactions (“selenoprotein” specifically denotes a protein that requires Se at the active site in the form of SeCys for functional activity).

Because selenomolecules are metabolized by species-specific pathways, the physiologic benefit of Se consumption to an animal depends in part on the chemical forms that are consumed. Selenite, selenate, and SeCys are metabolized to selenide, and Se from these compounds is efficiently incorporated into selenoproteins (i.e., proteins such as glutathione peroxidase that require Se for catalytic activity).<sup>5</sup> However, selenoprotein expression is homeostatically regulated, so the total amount of Se that accumulates in this pool is tightly regulated and maximized at relatively low intakes of Se. Alternatively, because SeMet randomly substitutes for Met, when SeMet is consumed Se will accumulate in large protein masses (e.g., in the albumin in plasma).<sup>5</sup> Some plants accumulate methylated forms of Se such as Se-methyl selenocysteine (SeMSC), which is easily cleaved by a specific lyase-generating methyl selenol.<sup>6</sup>

Methylated forms of Se enter directly into the methylation pathway—they do not accumulate in the body as much as SeMet, SeCys, or inorganic Se—and methylated forms of Se may provide superior chemoprotection against cancer.<sup>4</sup>

## SE BIOCHEMISTRY IN PLANTS

Biochemical transformations of Se in plants have been studied extensively and are reviewed in detail elsewhere.<sup>7,8</sup> Plants absorb Se from soil primarily as selenate and translocate it to the chloroplast, where it follows the sulfur assimilation pathway. There it is activated by ATP sulfurylase to form adenosine-5'-phosphoselenate. From this point, Se is reduced (enzymatically and non-enzymatically) to selenide, which reacts with serine to form SeCys. SeCys can be further metabolized to SeMet and methylated to form products such as Se-methyl Met. Alternatively, SeCys-specific methyl transferase may form SeMSC, allowing the plant to accumulate extraordinarily large amounts of Se.<sup>9</sup>

There is limited evidence that plants contain selenoproteins. Fu et al.<sup>10</sup> confirmed that SeCys was incorporated into glutathione peroxidase in *Chlamydomonas reinhardtii* by a mechanism very similar to that described in animals. Others have reported the existence of homologs of other selenoproteins, including phospholipid hydroperoxide glutathione peroxidase, selenoprotein W, and selenoprotein-like polypeptides in *C. reinhardtii*<sup>11</sup> and *Arabidopsis thaliana*.<sup>12</sup>

The chemical form of Se in plants can be determined by specialized techniques such as HPLC coupled to Se-specific detection by inductively coupled plasma mass spectrometry (ICP-MS)<sup>13</sup> or electron spray ionization-mass spectrometry (ESI-MS).<sup>14</sup> The most popular technique, HPLC-ICP-MS, uses conventional HPLC with either reverse-phase or ion-exchange columns to separate selenocompounds that are detected by an ICP-MS tuned on specific Se isotopes. This method eliminates interferences from similar, non-Se-containing compounds (e.g., it eliminates the interference of Met when attempting to detect SeMet). Presumptive identification is made by matching retention times to standard compounds.

A problem inherent in these techniques is that the compounds to be speciated must be removed from the matrix and, in the case of amino acids, from the protein complex. Michalke<sup>14</sup> has thoroughly reviewed problems associated with elemental speciation and commented that the increased sensitivity obtained with isolation and/or derivitization is often negated by changes in the chemical form of the analyte, leading to artifactual results. The stable isotope <sup>77</sup>Se gives a characteristic NMR signal, and growing plants in the presence of <sup>77</sup>Se-enriched

**Table 1.** Se and Cancer: Summary of Intervention Trials

Epidemiological Evidence	Location	Subjects	Cancer Type	Se Intervention	Results
SELECT <sup>50</sup>	United States, Puerto Rico, Canada	35,500 males age 50+	Prostate	<ul style="list-style-type: none"> <li>• 200 <math>\mu\text{g}</math> Se as SeMet for 12 yrs</li> <li>• 400 mg vitamin E + Se</li> <li>• Placebo</li> </ul>	In progress
Multiple prostate cancer trials <sup>51</sup>	United States	100–700 elderly men	Prostate	Selenized yeast (200–800 $\mu\text{g}$ Se/d)	In progress
Nutritional prevention of cancer trials <sup>3</sup>	United States	1312 men and women ages 18–80 yrs	Multiple	Selenized yeast (200 $\mu\text{g}$ Se/d for 10 yrs)	Significant reduction of all cancer incidence/mortality; specific reduction of prostate, colorectal, and lung cancers
Blot et al. <sup>52</sup>	China	29,584 men and women	Esophageal and gastric	Multiple nutrients, including beta carotene, vitamin E, and Se for 12 yrs	Beta carotene, vitamin E, Se was only treatment to significantly lower cancer rates
Yu et al. <sup>53</sup>	China	<ul style="list-style-type: none"> <li>• 130,471 residents of one county (observational study)</li> <li>• 226 HBV-positive persons (placebo control trial)</li> </ul>	Liver	<ul style="list-style-type: none"> <li>• 200 <math>\mu\text{g}</math> Se/d as selenized salt</li> <li>• 200 <math>\mu\text{g}</math> Se/d as selenized yeast</li> </ul>	<ul style="list-style-type: none"> <li>• 35% decrease in liver cancer</li> <li>• Decrease in liver cancer</li> </ul>

sources of Se may provide a unique means of speciating multiple selenocompounds without the need for extensive sample preparation.<sup>15</sup>

### SPECIFIC SE-ENRICHED PLANTS

Se-enriched plants may be divided into two broad groups. Plants that accumulate Se in direct relation to the amount of Se in the soil include most grains. For example, wheat grown in the United States normally contains 0.2 to 0.4  $\mu\text{g/g}$  Se; however, wheat grown in Se-rich soils may contain between 5 and 15  $\mu\text{g/g}$  Se.<sup>16,17</sup>

Plants that hyper-accumulate Se include garlic and broccoli. Under some conditions, Se concentrations may exceed 1 mg Se/g dry plant tissue.<sup>18,19</sup> There are limited reports about the chemical forms of Se in these plants,

but the available information suggests that the Se is often in methylated forms such as SeMSC,  $\gamma$ -glutamyl SeMSC, selenocystathione, selenohomocysteine,  $\gamma$ -glutamyl selenocystathione, and methyl selenol.<sup>7</sup> These forms of Se may be safely stored in membrane-bound structures within the plant; Se hyper-accumulators have a relatively small percentage of their total Se sequestered in the protein fractions of the plant.

### Vegetables

High-Se garlic has been extensively studied because of its efficacy for the reduction of mammary tumors in laboratory animals (for review, see Ip, 1998<sup>20</sup>). Se-enriched garlic contains Se primarily as  $\gamma$ -glutamyl SeMSC.<sup>18</sup> It is hypothesized that the efficacy of Se from

**Table 2.** Examples of Plants that are Se Accumulators or Hyper-Accumulators

Plant	Se Concentration ( $\mu\text{g/g}$ )	Chemical Form	Reference
<b>Accumulators</b>			
Wheat	0.1–15	SeMet	Olson et al., 1970 <sup>16</sup>
Brazil nuts	2.0–35+	SeMet	Vonderheide et al., 2002 <sup>42</sup>
Mushrooms	0.1–20	Unknown (not seleno amino acids or selenite)	Stijve, 1977 <sup>24</sup> ; Piepponen et al., 1983 <sup>26</sup>
Brussels sprouts	0.03–7.0	Unknown	Stoewsand et al., 1989 <sup>21</sup>
<b>Hyper-Accumulators</b>			
Garlic	>1200	SeMSC	Kotrebai et al., 2000 <sup>54</sup>
	<300	$\gamma$ -Glutamyl SeMSC	Kotrebai et al., 2000 <sup>54</sup>
Broccoli	~1000	SeMSC	Roberge et al., 2003 <sup>13</sup>
Ramp	>500	SeMSC (inorganic)	Kotrebai et al., 2000 <sup>54</sup>

SeMet = Selenomethionine; SeMSC = Se-methyl selenocysteine.

garlic for cancer prevention is due to SeMSC being quickly converted the putative anti-cancer metabolite methyl selenol.<sup>18</sup> Se from garlic does not accumulate in tissues to the same extent as Se from foods enriched in SeMet.<sup>20</sup>

*Brassica* spp. are the most studied edible Se accumulators. Species reported to accumulate Se include: broccoli (*Brassica oleracea*),<sup>19</sup> Indian mustard (*Brassica juncea*), Brussels sprouts (*Brassica oleracea* L.),<sup>21</sup> and canola (*Brassica napus*).<sup>22</sup> Se from high-Se broccoli is not as bioavailable as Se from salts or SeMet for restoration of tissue Se concentrations or selenoprotein activity in Se-deficient rats,<sup>23</sup> but is more effective than Se or broccoli alone for the reduction of chemically induced cancers in the intestines and colons of rats and mice.<sup>19</sup> *Brassica* spp., especially broccoli and canola, also have been used for phytoremediation, a process that uses Se hyper-accumulators to remove high (potentially toxic) concentrations of Se from soil and/or irrigation water.<sup>22</sup> In a single growing season, broccoli may extract up to 20% of soluble Se from Se-laden drainage water.<sup>22</sup>

### Microbial Sources of Se: Fungi, Algae, and Yeast

Although not true plants, mushrooms are generally grouped with vegetables for dietary purposes. Some but not all mushrooms accumulate Se. A survey of 83 species of wild mushrooms reported Se concentrations ranging from 0.01 to 20 ppm.<sup>24</sup> *Agaricus bisporus*, the button or portabella mushroom, is the most commonly consumed mushroom in the United States. It can accumulate very high concentrations of Se, and has been shown to be effective for the reduction of 7,12-dimethylbenz(a)anthracene (DMBA)-induced anti-3,4-dihydrodiol-1,2-epoxide-deoxyguanosine adducts in rats.<sup>25</sup> Other mushrooms that grow outside the United States and may accumulate Se include *Boletus edulis*<sup>24</sup> and *Boletus macrolepiota*.<sup>26</sup> A limited number of studies have reported

Se from mushrooms to have low bioavailability,<sup>27</sup> and it has also been reported to be present in low-molecular-weight compounds that are not SeCys, SeMet, or selenite.<sup>28</sup>

Se-accumulating marine plants have been studied primarily for their role in removing Se from agricultural runoff and contamination.<sup>29</sup> This Se is highly bioavailable, and animals that feed on these plants may exhibit signs of toxicity.<sup>30</sup> A few investigators have studied the blue-green algae *Spirulina platensis* as a possible source of Se/iodide pharmaceuticals.<sup>31</sup> Se in *Spirulina* has been reported to be in a high-molecular-weight form.<sup>32</sup> Overall bioavailability of Se from *Spirulina* was reported to be low, but an ultrafiltrable soluble fraction was highly bioavailable.<sup>32</sup> Se-enriched kelp is commercially available as a dietary supplement.

Although not a true plant and not generally considered to be a staple food, Se-enriched yeast is the most abundant commercially available source of supplemental Se, with at least a dozen products advertised on the Internet. Selenized yeast was the supplemental source of Se used in the cancer intervention study first reported in 1996.<sup>33</sup> SeMet is reported to be the primary chemical form of Se in yeast.<sup>15</sup> Because manufacturers of Se-enriched yeast do not adhere to a single production and/or quality standard, the form of Se probably varies considerably from product to product.

### Grains, Oilseeds, and Nuts

As a group, cereal grains are the most important source of Se in the western diet.<sup>34</sup> Se-enriched wheat has long been recognized as a source of supplemental Se for deficient populations. The Se status of residents of New Zealand, a region with very low concentrations of Se in the soil, increased following the importation of high-Se Australian wheat.<sup>35</sup> Se intakes in Finland were traditionally very low, and to increase them, the government instituted a national program of adding Se to all agricultural fertilizers. Increased Se concentrations were re-



ported in dairy products, beef, and cereal grains, and these changes were correlated with a 50% increase in blood Se concentrations.<sup>36</sup>

Reports of Se in oilseeds and nuts are limited. As noted, canola is a *Brassica* species and a Se accumulator.<sup>37</sup> Soybeans grown in high-Se areas of the country can be expected to contain relatively high concentrations of Se. In rats, the absorption of Se from soybeans was reported to be almost 20% less than Se from eggs, and 10% less than Se from sodium selenite.<sup>38</sup> Brazil nuts often are reported to be exceptionally good sources of Se, but the Se content varies greatly depending on where they are grown.<sup>39</sup> Se from Brazil nuts is bioavailable for restoration of Se concentrations and selenoprotein activity in Se-depleted rats, and has been reported to protect against chemically induced mammary cancer in mice.<sup>40</sup> SeMet has been reported to be the primary chemical form of Se in soybeans<sup>41</sup> and Brazil nuts.<sup>42</sup>

## MANIPULATION OF SE CONTENT IN PLANTS

Certain species of *Astragalus* may accumulate in excess of 2 mg Se/g plant tissue, and that Se often is in forms such as SeMSC,  $\gamma$ -glutamyl SeMSC, selenocystathione, selenohomocysteine,  $\gamma$ -glutamyl selenocystathione, and methyl selenol.<sup>43</sup> SeCys-specific methyltransferase is the enzyme needed for production of many of these compounds, and insertion of the gene for this enzyme into an *Astragalus* species that does not accumulate Se converts the plant to a Se hyper-accumulator.<sup>44</sup> Recently, this gene has been inserted into Arabidopsis, allowing accumulation of SeMSC and  $\gamma$ -glutamyl SeMSC.<sup>45</sup> Use of such technology may eventually allow the development of foods of dietary importance, such as grains and vegetables, with the ability to accumulate Se in methylated forms.

## VARIABILITY IN SE CONTENT OF PLANT FOODS

As previously noted, the Se content of plants is quite variable depending on where they are produced. When multiple brands of the same food were analyzed, the Se content often differed by an order of magnitude or more.<sup>46</sup> For example, 100 g of one brand of corn tortilla chips contained 2.1  $\mu$ g of Se (approximately 4% of the RDA), whereas the same portion of another brand contained 35  $\mu$ g of Se (64% of the RDA).<sup>46</sup>

Variability is particularly pronounced in grain products. In one study,<sup>47</sup> pasta products made in the United States were shown to contain 57  $\mu$ g Se/100 g, and a 100-g serving would supply 104% of the RDA. Conversely, pasta made in Italy averaged only 6  $\mu$ g Se/100g, and a similar serving would supply only 11% of the RDA.<sup>47</sup>

The variability of Se content of foods makes nutrient database values particularly suspect, especially when they are used to specify the Se content of a particular food. For example, the USDA National Nutrient Database value for Se in pasta is 20 to 24  $\mu$ g/100 g serving. A blend of multiple brands of American and Italian-made pastas results in a product with a Se content very near the value predicted by the database (Keck A-S, Finley JW, unpublished data), but the actual Se content of an individual diet made with a single brand of pasta could be very much under- or overestimated. The discrepancy in database values also is particularly problematic for plants that are minor dietary constituents (e.g., flaxseed).<sup>47</sup>

## INTERACTIONS BETWEEN SE AND OTHER DIETARY CONSTITUENTS

An unanticipated effect of increasing the Se content of *Brassica* spp. has been reports of reductions in glucosinolate production. The addition of 1 mg Se (as sodium selenate) per liter of water to broccoli grown by hydroponics resulted in decreased production of the sulforaphane precursor 4-methyl-sulphinylbutyl; the addition of 9 mg Se/L water decreased total glucosinolate concentrations to 33% that of control plants grown without Se.<sup>47</sup> Robbins et al.<sup>48</sup> reported that Se fertilization of broccoli decreased production of numerous glucosinolates and phenolic acids. Broccoli fertilized with sodium selenate had a Se concentration in the inflorescence of over 700  $\mu$ g Se/g dry weight, but the sulforaphane content was only 4% that of unfertilized controls. Additionally, the total and aliphatic glucosinolate and glucoraphanin concentrations were significantly reduced (although not to the extent of sulforaphane). Phenolic acids were also reduced in the Se-fertilized plants, with the greatest reductions in hydroxy-cinnamic esters.

There is evidence of an interaction between Se and glucosinolates from broccoli in animals that consume Se-enriched broccoli. Sulforaphane induces the selenoprotein thioredoxin reductase,<sup>49</sup> and the total activity of this protein is reported to be affected by a synergistic interaction of dietary Se and sulforaphane. The physiologic implications of upregulated thioredoxin reductase are unclear.

## CONCLUSIONS

Se supplementation of populations with low or deficient Se intakes may improve many measures of health, and supplementation of Se to populations with adequate intakes may reduce the risk of cancer. This is a compelling argument for augmenting the food supply with Se, and Se-enhanced plants may be the best means of ac-

complishing this. Plants accumulate varying amounts of Se in different chemical forms, and these factors must be taken into account when devising diets or supplementation schemes. The Se content of plants may be enhanced by genetic or environmental manipulations, but possible metabolic interactions within the plant or the human that consumes the plant must be evaluated.

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